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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/591,965	09/07/2006	Luisella Calabi	B358-US	4955

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EXAMINER	
GAKH, YELENA G	

ART UNIT	PAPER NUMBER
1797	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,965	CALABI ET AL.	
	Examiner	Art Unit	
	Yelena G. Gakh, Ph.D.	1797	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☒ Claim(s) *1,2* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09/07/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Specification

1. The disclosure is objected to because of the following informalities: on page 5, line 14, the word "fact" is misspelled; on page 17, line 27 the word "instance" is misspelled and "o" on the last line appears to be extra. Appropriate correction is required.

Claim Objections

2. Claim 1 is objected to because of the following informalities: recites "the said" in front of "exogenous or endogenous" - either "the" or "said" should be deleted. Appropriate correction is required.

3. Claim 2 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 2 recites the steps, which are inherent to claim 1, since in order to perform the steps of selection ore a suitable shift reagents, it is not necessary to perform the steps recited in claim 2.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a combination of specific shift reagents and endogenous or exogenous species, as well as nuclei, e.g. acetylsalicylic acid as the exogenous species and Dy-BOPTA as the shift reagent using ^{1}H MAS-NMR, does not reasonably provide enablement for method for all possible endogenous and exogenous species recited in the claims using all possible shift reagents recited in claims 10 and 11 and using MAS-NMR techniques with various nuclei. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. It

would have been an undue experimentation for a practitioner in the art to perform the steps of claim 2 in order to perform the method of claim 1, i.e. "a) identify a set of possible SA candidates for said SA and nucleus combination, on the basis of the LIS produced on at least one NMR signal belonging to said exogenous or endogenous substance; b) identify a set of possible candidates for said SA, on the basis of the CC/s in which they distribute; and c) select said SA and nucleus combination, on the basis of the information gathered from steps (a) and (b)" with an infinite number of possible combinations for such sets, and especially taking into account the following excepts from the specification:

> "The above MAS-NMR technique has been applied to the determination of the permeability of human blood cells by Magnetic Resonance Imaging Contrast Agents (MRI-CAs), particularly polyamino polycarboxylic Gd based contrast agents. This method comprises the use of a lanthanide complex able to produce a clearly detectable lanthanide induced shift (LIS) and a very weak relaxation (line broadening) on NMR signals of intra- and extra-cellular water protons. The rationale for this method relies on the complete isostructurality between the Gd-contrast agents (CA), which intra- or extra-cellular concentration has to be determined, and the lanthanide complex acting as shift agents (LIS agent). In other words, as both CA and LIS agent are supposed to show a very similar behavior (because of their isostructurality), the actual determinations of where the LIS agent is, i.e. its exact intra- or extra-cellular concentration, are deemed to substantially correspond to where the CA would be and to the CA intra- or extra-cellular concentration, respectively." (Page 5, lines 29-32, page 6, lines 1-9).

Furthermore,

> "The use of a SA for cellular uptake measurements, in fact, is based on and may only be advantageously applied when the signals of interest, corresponding to the given EXO (or ENDO) in the intra- and extra- CCs, are both detectable and well separated, to allow a reliable measure of their areas wherein this means that no overlapping can exist. Moreover, the said signals must be due to the 100% of the EXO (or ENDO) in the sample. This means that the whole signal has to be completely detectable, "visible", with respect the spectrum base line." (Page 10, lines 6-12),

and

> "In other words, in the method of the invention the presence of the SA may only determine a shift of the NMR signal of a substance when this same substance is very close to the SA, i.e. when both EXO and SA stay in the same cellular compartment. In this case, the measured LIS is a quantity directly linked to the absolute concentration of the analysed EXO in the different CCs, and its value is proportional to the ratio between the EXO and SA concentrations, hereinafter indicated as ρ^{EXO}=[SA]/[EX0]."

It appears that the condition for a successful output in performing the method, i.e.

> "To identify the most suitable set of SAs and nuclei combination for the quantitative determination of the cellular uptake of a given EXO, the said EXO is dissolved in D_20 and, by

> employing a variety of combinations of different SAs with different nuclei and by varying the ratio ρ^{EXO} = [SA]/[EXO], LIS^{EXO} signals are thus measured.
> SAs and nuclei combinations inducing the largest LIS^{EXO} signals are those most suitable for use with the EXO under investigation. Said largest LIS^{EXO} signal/s, hereinafter referred to as $marker^{EXO}$ signal/s, has/have to be considered as preferred according to the invention". (Page 13, lines 1-9).

will cause an undue experimentation for a practitioner in the art, since there are too many combinations of different nuclei, SA and ratios ρ^{EXO}. The specification does not appear to give any guidance to a routineer in the art, how such combinations should be searched. Furthermore, it is not apparent, as to how the best SA is chosen for a specific EXO/ENDO analyte under investigation, which makes the scope of enabled method unclear. The situation is complicated by the following possibilities:

> "if EXO and SA distribute into more than one CC (as per Figures 3c-3h; 4c-4h), the possibility of determining all of the EXO compartmental concentrations may require additional stoichiometric calculations which complexity may vary for the different situations, depending from the availability of some or all of the CC volumes and the number of CCs where SA and EXO distribute. In any case, by means of LIS^{EXO} signal vs. ρ^{EXO} graph, the values of the EXO compartmental concentrations can be calculated. To sum up, step (3) of the method of the invention is carried out by taking into account the CC/s where EXO stay, the volume/s of said CC/s, the value/s of the area/s under the $marker^{EXO}$ signal/s, the calculated ρ^{EXO} for every CC in which EXO stays, and by solving the system of equations connecting these parameters." (Page 17, lines 13-24).

The only real Example 2 does not show, how Dy-BOPT was selected for acetylsalicylic acid (ASA) and whether this SA is known to be the best for ASA. Furthermore, ASA appears to be a very simple compound and is not exemplary for the possible analytes recited in the claims.

6. Claim 14 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 14 recites "the method according to any one of claims 1 to 3, wherein for the kinetic parameters of cellular uptake are determined. The examiner failed to find any disclosure of determination of kinetic parameters in the specification.

The examiner respectfully reminds the Applicants that according to MPEP §2163:

> **"2163.02. Standard for Determining Compliance with Written Description Requirement**:

> The courts have described the essential question to be addressed in a description requirement issue in a variety of ways. An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Under *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting In re Kaslow, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)). Whenever the issue arises, the fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").

The Applicants failed to "show possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention".

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 13 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 provides for the use of method recited in claim 1, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is

intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 13 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim 14 omits all steps necessary for determining kinetic parameters of cellualr uptake, which renders the claim unclear and indefinite.

Claim Rejections - 35 USC § 102/103

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. **Claims 1-7, 10-12** are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Calabi et al. (J. Magn. Reson., 2002, IDS) (Calabi).

Calabi teaches "[a] new method, based on proton high-resolution magic-angle spinning (^{1}H HR-MAS) NMR spectroscopy, has been employed to study the cell uptake of magnetic resonance imaging contrast agents (MRI-CAs). The method was tested on human red blood cells (HRBC) and white blood cells (HWBC) (*Claim 12*) by using three gadolinium complexes, widely used in diagnostics, Gd-BOPTA, Gd-DTPA, and Gd-DOTA, and the analogous complexes obtained by replacing Gd(III) with Dy(III), Nd(III), and Tb(III) (*Claims 1-7, 10-11 and 13*) (i.e., complexes isostructural to the ones of gadolinium but acting as shift agents). The method is based on the evaluation of the magnetic effects, line broadening, or induced lanthanide shift (LIS) caused by these complexes on NMR signals of intra- and extracellular water." (Abstract). Thus, Calabi select three SA candidates and performs MAS-NMR spectroscopy to determine the compartmental concentration of said exogenous substance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yelena G. Gakh, Ph.D. whose telephone number is (571) 272-1257. The examiner can normally be reached on 9:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Vickie Y. Kim can be reached on (571) 272-0579. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Yelena G. Gakh/
Primary Examiner, Art Unit 1797

8/4/2009